

## REMARKS

In the Office Action Summary of the instant Action, Claims 1-38 are listed as pending in the application, of which Claims 6, 7 and 9-38 are listed as withdrawn from consideration, Claims 1-5 and 8 are listed as rejected. In response thereto, and without in any way acquiescing to the Examiner's reasoning but solely to put this application in condition for allowance, Applicants have amended herein Claims 1, 4-8 and 10-13. Applicants expressly reserve the right to either file a subsequent application directed to any cancelled subject matter or to introduce same into the instant application.

- Claim Rejections Under 35 U.S.C. §112, Second Paragraph

In the instant Action, Claims 4-5 are rejected under 35 U.S.C. §112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner alleges at page 3 of the instant Action that

" ... For example in claim 4, the species Ac-Gly1-hGhrelin (1-5) does not conform with the requirement of claim 1. Moreover, claim 5 recites Asp3(-O-hexyl)-hGhrelin (1-28) that does not conform to the requirements of residue A3. ... Claim 5 does not properly limit claim 4. Claim 5 recites Cys3(S-(CH<sub>2</sub>)<sup>9</sup>-CH<sub>3</sub>)-hGhrelin (1-28). This species does not appear in claim 4."

In response thereto, and without in any way acquiescing to the Examiner's reasoning but solely to put this application in condition for allowance, Applicants have deleted the compounds which are expressly objected to by the Examiner and additional compounds which are not expressly objected to by the Examiner, but which Applicants believe are implicitly objected to by the Examiner, as follows (without markings to show deletions):

In Claim 4

(Glu<sup>3</sup>(O-Hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:86)

(Aib<sup>1</sup>, Glu<sup>3</sup>(O-Hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:88)

(Ac-Gly<sup>1</sup>)hGhrelin(1-5)-NH<sub>2</sub>; (SEQ ID NO:90)

(Ac-Gly<sup>1</sup>)hGhrelin(1-6)-NH<sub>2</sub>; (SEQ ID NO:91)

(Ac-Gly<sup>1</sup>)hGhrelin(1-7)-NH<sub>2</sub>; (SEQ ID NO:92)

(n-Butyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(n-Butyryl-Gly<sup>1</sup>, Aib<sup>2</sup>, Glu<sup>3</sup>(NH-Hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:101)

(Isobutyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(n-Octanoyl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 5

(Thr<sup>6</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:102)

(Asp<sup>3</sup>(NH-heptyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:105)

(Aib<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:107)

(Glu<sup>3</sup>(O-hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:106)

(Asp<sup>3</sup>(O-hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:105)

Cys<sup>3</sup>(S(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:108)

(Lys<sup>5</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:110)

(Ac-Gly<sup>1</sup>)hGhrelin(1-5)-NH<sub>2</sub>; (SEQ ID NO:90)

(Ac-Gly<sup>1</sup>)hGhrelin(1-6)-NH<sub>2</sub>; (SEQ ID NO:91)

(Ac-Gly<sup>1</sup>)hGhrelin(1-7)-NH<sub>2</sub>; (SEQ ID NO:92)

(n-Butyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 6

(Ac-Gly<sup>1</sup>)hGhrelin(1-5)-NH<sub>2</sub>; (SEQ ID NO:90)

(Ac-Gly<sup>1</sup>)hGhrelin(1-6)-NH<sub>2</sub>; (SEQ ID NO:91)

(Ac-Gly<sup>1</sup>)hGhrelin(1-7)-NH<sub>2</sub>; (SEQ ID NO:92)

(n-Butyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(Isobutyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(n-Octanoyl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 7

(Ac-Gly<sup>1</sup>)hGhrelin(1-5)-NH<sub>2</sub>; (SEQ ID NO:90)

(Ac-Gly<sup>1</sup>)hGhrelin(1-6)-NH<sub>2</sub>; (SEQ ID NO:91)

(Ac-Gly<sup>1</sup>)hGhrelin(1-7)-NH<sub>2</sub>; (SEQ ID NO:92)

(n-Butyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(Isobutyryl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

(n-Octanoyl-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 8

(Glu<sup>3</sup>(O-Hexyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:106)

(Cys<sup>3</sup>(S-Decyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:108)

In Claim 10

(Aib<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:116)  
(n-Octanoyl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Isobutyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(n-Butyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Aib<sup>1</sup>, Thr<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:122)  
(n-Octanoyl-Gly<sup>1</sup>, Thr<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:132)  
(Isobutyryl-Gly<sup>1</sup>, Thr<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:132)  
(n-Butyryl-Gly<sup>1</sup>, Thr<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:132)  
(Ac-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Ac-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 11

(Aib<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:107)  
(n-Octanoyl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Isobutyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(n-Butyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 12

(Aib<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:107)  
(n-Octanoyl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Isobutyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(n-Butyryl-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

In Claim 13

(Ac-Gly<sup>1</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)  
(Ac-Gly<sup>1</sup>, Ser<sup>3</sup>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:100)

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of Claims 4-5, and implicitly the rejection of Claims 6-8 and 10-13, under 35 U.S.C. §112, second paragraph.

- Claim Rejections Under 35 U.S.C. §102

In the instant Action, Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Kangawa et al. (WO 01/07475). Specifically, the Examiner alleges at page 4 of the instant Action that

“the reference teaches Arg8-hGhrelin (1-8), that meets the limitation of claim 1 ... This meets the limitation of the claims when A1 is Gly, A2 is Ser, A3 is Ser(C(O)-R4), A4 is Phe, A5 is Leu, A6 is Ser, A7 is Pro, A8 is Arg, the rest of the A variables are absent. Note that A8, Arg is one of the substitutions that is required by the claim.”

In response thereto, and without in any way acquiescing to the Examiner’s reasoning but solely to put this application in condition for allowance, Applicants have amended the *proviso* clause which is appended to Claim 1, as follows (with markings to show deletions):

provided that the peptide contains at least one amino acid selected from the groups consisting of:

A<sup>2</sup> is Aib, Acc, or Act;

A<sup>3</sup> is Dap(S(O)<sub>2</sub>-R<sup>10</sup>), Dab(S(O)<sub>2</sub>-R<sup>11</sup>), or Glu(NH-Hexyl), ~~or Cys(S-Decyl)~~;

A<sup>5</sup> is Abu, Acc, Aib, ~~Ala~~, Cha, ~~He~~, hLeu, Nle, Nva, ~~Phe~~, or Tle, ~~or Val~~;

A<sup>6</sup> is Abu, Acc, Act, or Aib, ~~Ala, Gly, Thr or Val~~;

A<sup>7</sup> is Dhp, Dmt, 3Hyp, 4Hyp, Inc, Ktp, Oic, Pip, Thz or Tic;

A<sup>8</sup> is Acc, Aib, ~~Arg~~, Asn, Asp, Dab, Dap, ~~Gln, Lys, Orn~~, or HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>12</sup>R<sup>13</sup>))-C(O);

A<sup>9</sup> is Aib, Acc, Apc, 2Fua, 2Pal, 3Pal, 4Pal, Taz, 2Thi, 3Thi, or (X<sup>1</sup>,X<sup>2</sup>,X<sup>3</sup>,X<sup>4</sup>,X<sup>5</sup>-)Phe; and

A<sup>10</sup> is Acc[[,]] or Aib, ~~Asn, Asp, or Glu~~;

Firstly, it should be noted that Applicants have amended the *proviso* clause of Claim 1 to require that at least one of the substitutions is a synthetic, unnatural amino acid such as Aib, Dap, Pal, Phz, etc. In contrast, the cited reference does not teach or suggest analogs of human ghrelin where at least one of the substitutions is a synthetic, unnatural amino acid.

More importantly, in order to completely remove overlap with the cited reference as noted by the Examiner, Applicants have deleted “Arg” from A8 of the formula (I), as follows (with markings to show deletions):

A<sup>8</sup> is Glu, Acc, Aib, ~~Arg~~, Asn, Asp, Dab, Dap, Gln, Lys, Orn, HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>12</sup>R<sup>13</sup>))-C(O), or deleted;

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 1 under 35 U.S.C. §102(b) as being unpatentable over Kangawa et al. (WO 01/07475).

- Claim Rejections Under 35 U.S.C. §103

In the instant Action, Claims 1-5 and 8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kangawa et al. (U.S. Patent No. 7,385,026). Specifically, the Examiner alleges at page 5 of the instant Action that “the reference teaches hGhrelin of the sequence Cys<sup>3</sup>(octyl)-hGhrelin.”

First, it should be noted that Applicants have deleted “Cys(S-Decyl)” from A3 of the *proviso* clause.

More importantly, in order to completely remove overlap with the cited reference as noted by the Examiner, Applicants have deleted “Cys(S-R<sup>14</sup>)” from A3 of the formula (I), as follows (with markings to show deletions):

A<sup>3</sup> is Ser, Ser(C(O)-R<sup>4</sup>), Asp(O-R<sup>8</sup>), Asp(NH-R<sup>9</sup>), ~~Cys(S-R<sup>14</sup>)~~, Dap(S(O)<sub>2</sub>-R<sup>10</sup>), Dab(S(O)<sub>2</sub>-R<sup>11</sup>), Glu(O-R<sup>6</sup>), Glu(NH-R<sup>7</sup>), Thr, Thr(C(O)-R<sup>5</sup>), or HN-CH((CH<sub>2</sub>)<sub>n</sub>-N(R<sup>12</sup>R<sup>13</sup>))-C(O);

The Examiner further alleges at pages 5-6 of the instant Action that “claims 2-4 have been rejected since claim 5, which is dependent on claims 2-4, contains the Cys-containing Ghrelin analog. These claims have been rejected since it has been assumed that claims 2-4 required Cys-containing Ghrelin analog but were inadvertently omitted from the claims.

As noted above, Applicants have deleted all such “Cys-containing Ghrelin analog” – *i.e.*, Cys<sup>3</sup>(S(CH<sub>2</sub>)<sub>9</sub>CH<sub>3</sub>)hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:108) – from Claim 5. In fact, in order to ensure that the Examiner’s concern is fully addressed, Applicants have deleted “(Cys<sup>3</sup>(S-Decyl))hGhrelin(1-28)-NH<sub>2</sub>; (SEQ ID NO:108)” from Claim 8, as also noted above.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of Claim 1 under 35 U.S.C. §103(a) as being unpatentable over Kangawa et al. (U.S. Patent No. 7,385,026).

Examiner Gupta is invited to telephone Applicants’ undersigned attorney to facilitate prosecution of this application.

Prompt and favorable action is solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Tony K. Uhm', with a horizontal line drawn underneath it.

Tony K. Uhm (Reg. No. 52,450)  
Attorney for Applicants

Biomeasure, Incorporated  
27 Maple Street  
Milford, MA 01757-3650  
TEL.: (508) 478-0144  
Fax: (508) 478-2530